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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 06/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/743,516	Applicant(s) BRADDOCK ET AL.	
	Examiner Scott Priebe	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15 and 23-39* is/are pending in the application.

4a) Of the above claim(s) *39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 23-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 4/18/02 has been entered. Claims 1-14 and 16-22 have been cancelled. Claim 15 has been amended, and claims 23-39 have been added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

Newly submitted claim 39 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Original claims 1-13 were directed to the use of a nucleic acid molecule in the manufacture of a pharmaceutical, not to a method of therapy. Original claim 15 was directed to a pharmaceutical composition comprising a nucleic acid molecule. and original claim 16 was directed to a method of gene therapy wherein a nucleic acid molecule is administered to a mammal; which is *in vivo* gene therapy classified in 514/44. Amended claims 15 and new claims 23-38 are directed to a method of gene therapy wherein a composition comprising a nucleic acid molecule or a nucleic acid molecule is administered to a mammal; which is *in vivo* gene therapy classified in 514/44. New claim 39 is directed to a method wherein a cell comprising the nucleic acid molecule is administered to the mammal; which is *ex vivo* gene therapy and classified in 424/93.21. These two types of gene therapy, *in vivo* and *ex vivo*, are different methods requiring different materials, nucleic acid vs. recombinant cells, and different methods, and different

considerations with respect the requirements of §112, §102, §103. Both methods use nucleic acid molecules at some point, however, the nucleic acid molecules where known in the prior art. The full search of each is not required for the other, and a search of the art on these two types of gene therapy are not coextensive.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 39 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Drawings

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 4/18/02 have been approved. A proper drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The correction to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

Claim 15 remains rejected and claims 23-38 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record applied to claims 1-16 set forth in the Office action of 1/18/02, as containing subject matter which was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 4/18/02 have been fully considered but they are not persuasive. Applicant asserts that the specification teaches how to make vectors. However, given that this information was already well known in the art, and gene therapy is a highly unpredictable, and as yet, a largely unsuccessful art, as shown by Orkin, this information does not guide one skilled in the art on practicing the claimed invention successfully. It does not teach how to solve any of the problems that plague this art.

Page 14, lines 27-29 teach that the nucleic acid be administered to the wound site or tissue in need of healing; page 15, line 30 to page 16, line 5, merely discusses methods of administering nucleic acids, not where the nucleic acids should be administered. First, claim 15 is not limited to any particular site of administration. Second, this guidance does not suggest that the nucleic acid be administered prior to wound formation or prior to the time a tissue is in need of healing. In teaching administering the nucleic acid molecule to a wound or to tissue in need of healing, the specification is clearly teaching administration of the nucleic acid to the tissue AFTER the damage has been done, e.g. after wound formation. Page 28, lines 17-20, essentially teaches that any route of administration can be used if it is "effective for targeting wound sites", but the specification does not teach how to target wound sites other than administration directly to the wound site. There is no teaching on how to deliver the nucleic acid to a site separate from a

wound and have the nucleic acid molecule transfect cells at the wound. Claims 23-38 are limited to direct administration to a wound site, and this particular issue does not apply.

Applicant points to page 4, lines 4-5 as teaching when the nucleic acid molecule should be administered. This passage merely asserts that the invention can be used to reduce scarring during healing. It does not teach when, relative to wound formation, the nucleic acid molecules should be administered. It is not clear what the citation of Shah et al. in this passage is meant to convey; the specification does not refer to any teaching in the reference to explain why it was being cited. Shah discloses a study on the effects of administering an antibody to TGF-β1,2, not a nucleic acid encoding NAB1 or NAB2. Furthermore, mere reference to a publication is not an incorporation of anything into an application for the purpose of disclosure required by §112, see MPEP 608.01(p). The specification does not teach explicitly or implicitly that the nucleic acid molecules "should be delivered early in the healing process," and Shah cannot be relied upon to provide such teaching. Applicant also points to Example 4 as teaching that the nucleic acid molecules be delivered prior to wounding. However, nowhere does the specification bring any attention to pre-treatment with the nucleic acid molecule as being a treatment option. Example 4 presents three conclusions: 1) delivery of the NAB2 cDNA did not impair healing (page 35, lines 34-35; 2) delivery of the NAB2 cDNA caused a decrease in TGF-β1 (marginal) and an increase in TGF-β3 and in granulation tissue, and that NAB2 *may* have anti-scarring properties as a result (page 36, lines 26-30); and 3) NAB2 blocked EGR-1 stimulated activation of angiogenesis. However, the actual effect on scarring was not assessed, and Applicant did not conclude that the

procedure in Example 4 *would* reduce scarring, which is the only "cell proliferation disorder associated wound healing" mentioned in the specification. Furthermore, the claims recite that the nucleic acid molecule is administered "to a wound site of the mammal", not to a site that will be a wound site. Consequently, administration of the nucleic acid molecule to a future wound site is not embraced by the claims. The problem remains of when to deliver the nucleic acid molecule "to a wound site" so that sufficient NAB1 or NAB2 is produced in time to inhibit EGR-1. A problem not addressed, much less solved, by the specification.

Applicant points to page 29, lines 3-11 and page 33, lines 4-14 as teaching appropriate dosage of nucleic acid molecules. This general teaching does not distinguish between protein compositions and nucleic acid compositions, nor does it distinguish between various modes of administration, such as systemic delivery vs. delivery directly to the wound site; and the dose range is 1000-fold. The effect of a given weight of protein and given weight of nucleic acid encoding that protein are not comparable in the absence of knowing how much protein would be produced in a cell transfected with the nucleic acid or whether the weight of nucleic acid refers only to that encoding NAB1 or NAB2, or includes vector backbone sequence as well. The specification is devoid of teaching on the amount of NAB1 or NAB2 protein per amount of tissue at a wound site required to reduce scarring. Page 33, lines 4-14 refers to an *in vitro* assay involving cells, not mammals. The specification does not teach how the amount of nucleic acid used in this experiment relates to treating a mammal. Example 4 involves a dose of between 0.002 to 0.006 mg nucleic acid/kilogram of rat, well below the lower limit mentioned on page 29.

Also, Example 4 does not include any qualitative or quantitative assessment of scar formation. Thus, the specific range of doses on page 29 is a guess since there is no working example that correponds to the claimed method; and the specification does not provide the basis upon which the guess was made. Applicant indicates that Example 4 would apply to cosmetic surgery, however, the specification mentions keloid formation following cosmetic surgery only as background. The specification does not provide any teachings on how the invention would be used specifically during cosmetic surgery, and Example 4 does not refer to cosmetic surgery and provides no assessment of scar formation. Example 4 shows a reduction in angiogenesis, but this was disclosed as being an indication that the treatment blocked growth factor activation, not that reducing angiogenesis was a desired therapeutic endpoint. Indeed, the specification does not teach that angiogenesis is a "cell proliferation disorder" that should be reduced. The specification teaches that ultimately the dose should reduce cell proliferation without preventing wound healing. However, the specification does not teach what that dose (or dose range) accomplishes this, nor provide an assessment of how broad the window is, nor provide a method for determining the proper dose. All of this is left for one of skill in the art to determine.

The prior art of record indicates that gene therapy was a highly unpredictable, and largely unsuccessful art at the time the invention was made. No evidence has been provided to the contrary. The teachings in the specification are general, essentially relying upon what had been used or done by others. The specification does not present any working example where the disclosed goal of the treatment, i.e. reduction of scarring without preventing healing, was

accomplished. At best the specification show one example, not readable on the claims, where pre-treatment with the nucleic acid did not prevent healing. The prior art disclosed that the therapeutic window for reducing scarring without preventing healing is very narrow in terms of timing administration and also likely in terms of the desired level of EGR-1. The specification does not address these problems or offer solutions.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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Art Unit 1632